Reassessing the Inclusion of Race in Diagnosing Kidney Diseases: An Interim Report From the NKF-ASN Task Force

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Abstract

For almost 2 decades, equations that use serum creatinine, age, sex, and race to estimate glomerular filtration rate (GFR) have included "race" as Black or non-Black. Given considerable evidence of disparities in health and health care delivery in African American communities, some

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regard keeping a race term in GFR equations as a practice that differentially influences access to care and kidney transplantation. Others assert that race captures important non-GFR determinants of serum creatinine and its removal from the calculation may perpetuate other disparities. The National Kidney Foundation (NKF) and American Society of Nephrology (ASN) established a task force in 2020 to reassess the inclusion of race in the estimation of GFR in the United States and its implications for diagnosis and subsequent management of patients with, or at risk for, kidney diseases. This interim report details the process, initial assessment of evidence, and values defined regarding the use of race to estimate GFR. We organized activities in phases: (1) clarify the problem and examine evidence, (2) evaluate different approaches to address use of race in GFR estimation, and (3) make recommendations. In phase 1, we constructed statements about the evidence and defined values regarding equity and disparities; race and racism; GFR measurement, estimation, and equation performance; laboratory standardization; and patient perspectives. We also identified several approaches to estimate GFR and a set of attributes to evaluate these approaches. Building on evidence and values, the attributes of alternative approaches to estimate GFR will be evaluated in the next phases and recommendations will be made.

The measurement of creatinine, the muscle protein metabolite, in serum is used to estimate kidney function as estimated glomerular filtration rate (eGFR) and has served as a major marker for the detection, diagnosis, and management of kidney diseases. Creatinine-based eGFR ($eGFR_{cr}$) thresholds guide clinical practice, including estimation of surgical complication risk; initiation, discontinuation, and dosing of medications; and utilization of certain contrast-based tests and procedures, such as computed tomography scans or cardiac catheterizations. Almost all clinical laboratories in the United States now report eGFR with any laboratory metabolic panel that contains serum creatinine, with one estimate for African Americans and another for non–African Americans.[1] Use of race in medical practice has come under scrutiny in light of the most recent reckoning with racism and publicly displayed atrocities against racial and ethnic minorities across the United States that has been longstanding.

On a national scale, eGFR is used for important surveillance and regulatory purposes, including population tracking of kidney diseases by the Centers for Disease Control and Prevention and the US Renal Data System, research supported by the National Institutes of Health (NIH) and other public and private funding agencies (including ongoing clinical trials), and eligibility for kidney disease education or nutritional supplementation under the Medicare program.[2–5] Although GFR estimation has remained an important guide for clinical decision making and population tracking, derived equations, like many other tools in medicine, have undergone a nearly 50-year history of re-evaluation, adaptation, and refinement. This evolution continues in the reassessment of the use of race in estimating GFR.

Evolution of Kidney Function Estimating Equations

Since 1976, equations developed to estimate the clearance or filtration function of the kidney from serum creatinine concentration have included, and adjusted for, various factors, including age, sex, African American race, and/or body weight. These equations were

largely developed using clinical, epidemiologic, and statistical methods that were, at the time of equation derivation, considered to be scientifically state of the art.

The Cockcroft-Gault equation, one of the initial equations, used data from 249 White men with measured creatinine clearance ranging from 30 to 130 mL/m^2 to estimate creatinine clearance.[6] Although this equation represents one of the initial attempts to approximate kidney function without needing to undergo laborious and potentially incomplete urine collection, the derivation cohort was limited by lack of both race and sex diversity.

Race in Estimated GFR Assessment in the United States

After the publication and use of the Cockcroft-Gault equation and before the derivation of subsequent equations, published research by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) showed that serum creatinine concentrations were higher among non-Hispanic Black adults when compared with non-Hispanic White adults.[7] This research was based on the Third National Health and Nutrition Examination Survey, a nationally representative sample of the US population. Subsequent research by Levey and others found that serum creatinine levels were higher among African American adults who had the same measured GFR as their White adult counterparts, indicating that determinants of serum creatinine levels, other than GFR, differed between the groups.[8]

Race was among the 16 factors considered in the derivations and refinement of the Modification of Diet in Renal Disease (MDRD) Study equation reported in 1999.[8] In regression models to predict GFR from serum creatinine levels, a term (and coefficient) for self-identified African American race was found to be a substantial and statistically significant predictor of carefully measured GFR.[8] The MDRD Study equation was validated in the African American Study of Kidney Disease and Hypertension.[9] At the time, this adjustment was thought to be an advance because an important group, with high risk for CKD progression, was included in studies of measured GFR.

In 2009, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using creatinine was developed in a subsequent analysis with pooled studies of individual participants. Meta-analytic regression was used in a more heterogeneous participant population, which combined data from thousands of individuals (including White, African American, and—to a far lesser extent—Asian, Hispanic/Latinx, and Native American individuals) from 10 different independent studies. Results were validated in a pooled group of 16 separate studies.[10] Across these studies, investigators found a similar result for African American race as a predictor of measured GFR, with the magnitude of the coefficient slightly less than that in the MDRD Study equation (1.20 compared with White individuals for the MDRD Study equation, and 1.16 compared with non-Black individuals for the CKD-EPI equation). In studies of measured GFR in the United States, other racial and ethnic groups were not included in large-enough numbers to understand whether differences in non-GFR determinants of creatinine are present in persons of non-White and non-Black race or ethnicity.[11]

An alternative filtration marker, cystatin C, is available and does not include race in its estimating equation for GFR. Estimated GFR from cystatin C is not more accurate than eGFR$_{cr}$; however, the equation reported in 2012, with a combination of the 2 markers, provides more accurate estimates.[12] A term for African American race is included in this combined marker equation that is sub-stantially smaller than in the creatinine-only equations (1.08). In the report of the equation, the investigators noted an insufficient number of African Americans were included in the validation datasets, prohibiting validation of the effect of this coefficient in a separate population outside of the development population.

Clinical practice guidelines from KDIGO (Kidney Disease: Improving Global Outcomes) recommend that, whenever serum creatinine is measured in clinical practice, an eGFR should be reported with an eGFR$_{cr}$, using the CKD-EPI 2009 creatinine equation or a similarly accurate equation. When a more accurate assessment of GFR is required, or there are concerns about the accuracy of eGFR$_{cr}$, this initial test should be followed by a confirmatory test using eGFR computed by cystatin C (alone or in combination with creatinine), measured creatinine clearance, or measured GFR.[13] Since the first eGFR equations were introduced 2 decades ago, data from laboratories in the United States show continual growth in the reporting of eGFR along with serum creatinine and, despite KDIGO guidelines, the MDRD Study equation is the most frequently used.[14]

Probing the Rationale for a Race Coefficient

Although the biological rationale for including coefficients (such as age, sex, and body weight) in eGFR equations seem apparent, the reasons for including race on the basis of serum creatinine observational data, muscle mass, and/or other factors are questionable.[15] It may be problematic to rely on a correction without completely understanding what factors are being captured together, and with an underappreciation of the ancestral diversity among African Americans that also exists in other racial and ethnic groups.[16] There is well-known exploitation and inhumane experimentation to which racial and ethnic minority individuals, particularly African Americans, have been subjected.[17] As a small, but growing, number of US individuals self-identify as being of mixed racial background, the complexity of a changing racial and ethnic composition makes the use of race in the practice of medicine further problematic. Recent calls for social justice reform have galvanized segments of the medical community into further discourse and action toward achieving greater health care equity, including the assertion of race as a social, nonbiological, construct.[18–24]

Many assert that removing race from estimating GFR would achieve better health and health care equity by mitigating disparities, particularly for African American patients who experience faster progression to kidney failure and lower rates of transplantation. This rationale posits that such a change would result in earlier identification and management of kidney diseases for African American patients, referral for specialist care by nephrologists, and earlier referral for kidney transplantation.[25–27] Others assert that, even if previously observed racial differences are poorly understood, race is capturing important determinants of estimated GFR. This rationale posits that removing race may create or perpetuate other disparities by assigning the value for non–African Americans to African Americans.[17,28,29] There is also a concern of subjectivity in regards to applying the African American race

coefficient on health care decision making, and personal and/or provider bias in transparency with patient-physician communication. These points of view, along with others, have highlighted the need to find an approach to GFR estimation that embraces the substantial diversity of the US population and promotes social and health equity without creating new, or worsening current, health disparities.

Disparities in Health and Health Care

Studies have shown disparities in health and health care disproportionately affect African Americans. When compared with non-Hispanic White individuals, African Americans have nearly double the prevalence of hypertension, a common etiology of kidney disease.[30–32] Decline in GFR among African Americans occurs at an earlier age and at a faster annualized rate when compared with non-Hispanic White Americans, even by cystatin C–based GFR assessment.[33] African Americans with advanced kidney disease are younger, with an incidence of kidney failure nearly 3 times that of their non-Hispanic White counterparts.[5]

Such disparities go beyond the burden of kidney diseases and extend into differences in kidney disease treatment. Before the widespread use of GFR estimation, it was documented that African Americans were more likely to receive a late referral for an evaluation by a nephrologist, a finding that is associated with decreased survival after the development of kidney failure.[34] As documented since the 1980s and 1990s, African Americans are less likely to be treated with home dialysis therapies and to be waitlisted for kidney transplant, with even fewer being transplanted.[5,35–38] The reasons for observed disparities are multifactorial and may be attributed to internalized, personal, or institutionalized racism.[39,40] To date, disparities in health and health care have not been conclusively attributed to race correction in eGFR equations, although research is ongoing.

Whereas Medicare spends approximately $120 billion annually on people with kidney diseases (including >$70 billion for people with kidney disease not requiring kidney replacement therapy), the NIH budget on kidney research is less than $700 million, and little has been allocated to the understanding of racial disparities in kidney disease care and outcomes.[5,41] Reassessing race in eGFR should be the start of reassessing race in other areas of diagnosis and management decisions related to kidney disease. Multi-faceted initiatives beyond an examination of GFR estimating equations are important to address, and ultimately eliminate, disparities.

Formation of the NKF-ASN Task Force

The National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) announced on July 2, 2020 plans to establish a task force to reassess the inclusion of race in diagnosing kidney disease. Representing patients, health care professionals, and other advocates across the world,[42] NKF and ASN are 2 leading organizations dedicated to preventing, treating, and ultimately curing kidney disease. During the past 2 decades, both organizations have championed health equity and health care disparities in kidney disease. The formation of the joint task force is a strong affirmation of both organizations' commitment to health equity, diversity, and scientific evidence.

A decision to remove race from the estimation of GFR is not trivial and could have consequences. As such, NKF and ASN charged the task force with:

- Examining the inclusion of race in the estimation of GFR and its implications for the diagnosis and subsequent management of patients with, or at risk for, kidney disease.

- Recognizing that any change in eGFR reporting must consider the multiple social and clinical implications, be based on rigorous science, and be part of a national conversation about uniform reporting of eGFR across health care systems.

- Incorporating the concerns of patients and the public, especially in marginalized and disadvantaged communities, while rigorously assessing the underlying scientific and ethical issues embedded in current practice.

- Ensuring that GFR estimation equations provide an unbiased assessment of GFR so that laboratories, clinicians, patients, and public health officials can make informed decisions to ensure equity and personalized care for patients with kidney disease.

- Keeping laboratories, clinicians, and other kidney health professionals apprised of any potential long-term implications of removing race from the eGFR formula.

The task force was created to include a variety of health professionals and patients, including individuals with expertise in diagnosis, management, and treatment of kidney disease; measurement and estimation of GFR; health care disparities; epidemiology and clinical research; laboratory medicine; pharmacy; health services research; patient safety; patient experience with care; patient quality of life; medical education; and prevention/ public health. The NKF and ASN leadership selected the cochairs and initial members, recognizing the need for various perspectives and backgrounds, requisite expertise, interest, and ability to commit to the intensive deliberations that lie ahead. The cochairs additionally suggested to NKF and ASN that they appoint patients, an expert in drug dosing and US Food and Drug Administration (FDA) considerations, and an expert on public health surveillance. Patients were explicitly included as members because of the importance of their voice and the effects any potential change could have on their health and well-being. Task force members are not remunerated. Disclosures are included in the Article Information at the end of this report.

NKF-ASN Task Force Process

During the initial meeting of the task force, members stated their familiarity and involvement with the issues and biases so that other members of the task force were aware of individual initial leanings. The task force then established principles to guide its interactions and deliberations, including: (1) embracing a holistic approach that examines the clinical, psychosocial, and financial tradeoffs of benefits and harms, balancing them across racial/ethnic groups with particular attention to how kidney diseases affect different races; (2) being data driven and generating a solution driven by science and evidence; and (3)

engaging in effective listening, respecting different ideas and opinions, and having a willingness to learn after hearing all perspectives.

Importantly, the NKF-ASN leadership and the members of the task force collectively agreed on the confidentiality of deliberations (including refraining from social media commentary) to promote candid opinions and exchange of ideas. Members also mutually agreed to work toward the goal of agreement in instances where there were differences of opinion. All task force weekly sessions were held virtually due to social distancing directives during the coronavirus disease 2019 pandemic.

To undertake a comprehensive and in-depth exploration of several issues germane to race and GFR estimation, the task force organized its activities into 3 phases (Box 1). This interim report focuses on phase 1.

Phase 1

In phase 1, the task force clarified the problem and evidence by examining information, including testimony, lectures, and literature from experts (Table 1). First, the members of the task force collectively identified and decided upon the domains to be considered and the panelists and discussants to be formally invited by the cochairs and NKF-ASN leadership to provide expert testimony. We sought a wide range of evidence and views, as illustrated by representation across the United States. We assured confidentiality to individuals who provided testimony, in some instances due to sharing of unpublished information. Members of the task force with subject matter expertise served as subject moderators so that no one task force member unduly influenced the entire process, an approach to be followed forward to final recommendations. Task force moderators devised goals for each session, an agenda, and an outline of specific questions for which the task force sought information. For example, a session on race and racism included an in-depth review of the definitions of race and racism, and the effect of internalized, personal, and institutional racism on health and health care disparities. The task force defined and discussed genetic ancestry and its relation with self-reported race; examined studies on the relation of genetic ancestry to serum creatinine levels; and evaluated the history of GFR measurement and the underlying physiology, study design, populations, and statistical methods used for the derivation of the most commonly used GFR estimating equations.

Equation examination included an intensive review of the race, ethnicity, and socioeconomic and clinical characteristics of participants in the studies incorporating the gold standard of direct measurement of GFR included in equation derivation. Substantial heterogeneity exists across individual studies and, therefore, the task force evaluated approaches for pooling data from different cohorts (ie, meta-analysis) for a more comprehensive and diverse sample of people for equation derivation. The task force also explored past efforts to achieve consistency in eGFR assessment and reporting across US clinical laboratories and institutions through standardization of laboratory measurements and promulgation of clinical practice guidelines. Finally, the task force considered patients' perspectives and the role of shared decision making in the delivery of health care. After each session, members of the task force debriefed privately to discuss and summarize invited testimony and independent literature reviewed. On the basis of this information, the task force developed a series of

statements that summarized the evidence and values held by its members regarding health and health care equity, disparities, race and racism, GFR, standardization, and patients' perspectives (Box 2). All members of the task force actively participated in constructing the statements of evidence and value, scrutinizing and revising them. Revisions included a series of iterations regarding content, language, and perspective.

The task force then assembled an inclusive inventory of potential approaches to GFR estimation or measurement that included approaches in which race is considered and not considered in derivation and/or reporting of eGFR (Box 3). The approaches included those (1) currently in widespread use (including race in eGFR equations), (2) recently adopted at some institutions, (3) currently available that might be amplified more broadly, and (4) recently suggested that are currently under development or could be developed.

Final recommendations will be made after the task force examines the strengths and weaknesses of existing and newer approaches to estimating GFR. The downstream consequences of changes from current reporting are unknown and could be profound. Changes could lead to overdiagnosis or underdiagnosis of kidney diseases as a result of GFR estimation bias and inaccuracy for any ethnic group. Conclusive evidence on outcomes from well-conducted studies will likely take years to produce. The resultant effects in terms of the numbers of African Americans affected and the safety and effectiveness of pharmacotherapy use and dosing need appraisal. Additionally, effect on managing risk factors (eg, hypertension), nephrology referral, transplant waitlisting, and kidney donation will also warrant evaluation.

The ramifications of changes in eGFR equations on research studies examining kidney diseases in African Americans and all other races/ethnicities, how such changes might affect US FDA approval and labeling of therapies, and the possible effect on the federal government's tracking of kidney diseases require further examination. The availability in communities of assays for newer biomarkers that do not use a race term (eg, cystatin C, β-trace protein, $β_2$-microglobulin) also need evaluation.[76,96]

Phases 2 and 3

Recognizing the use of race in estimating equations is problematic, the task force has focused on identifying a path forward. In phase 2, on the basis of testimony, lectures from additional experts, literature, and input from the community of interested individuals and organizations, the task force will evaluate each of the possible approaches that could be recommended with regard to its patient, clinical, health system, and societal effects (Items S1–S2). The deliberations and conclusions of these meetings will be presented in detail in the final report.

The task force held a series of forums in January 2021 to invite input from the broader kidney community.[97] Over the course of 3 sessions, the task force heard from (1) students and trainees; (2) clinicians, scientists, and other health professionals; and (3) patients, family members, and other public stakeholders. The task force also seeks input regarding the effect of particular approaches on patient safety and health equity put forth in this report (an online

feedback form is available at https://form.jotform.com/210244230676145). All of this information will be used to make future recommendations.

In phase 3, the task force will develop recommendations on the basis of a number of attributes (Box 4). These attributes include biomarker choice, inputs and their availability for estimation and reporting, representation of diversity in participants in research foundational to equation development, and equation bias and accuracy compared with measured GFR for different race and ethnic groups. Importantly, attributes also include consequences for clinical decisions with regard to evaluation and management of patients' GFR and feasibility of standardization. Finally, it is very important that any recommended approach incorporates the patient perspective and be patient centered.[98]

Recommendations will be reviewed and informed by an advisory board, including members of the NKF's and ASN's governing bodies, committees on diversity and inclusion, policy and advocacy panels, and experts in patient safety and health care quality. The task force is committed to continuing its transparent, open, and community-based process through phases 2 and 3.

Summary and Implications

Estimation of GFR is a major underpinning of many clinical decisions in medicine. The use of race to estimate GFR and possible replacements have shortcomings that the task force is currently examining. Nationwide, many institutions have made independent decisions to address race in estimation of GFR, but these approaches vary and, therefore, GFR estimates and subsequent care decisions are not standardized.

Because these differing approaches may have various effects for patients treated and followed by clinicians—including but not limited to primary care physicians, medical specialists (eg, nephrologists, hospitalists, endocrinologists, cardiologists, oncologists), surgical specialists, pharmacists, and public health professionals—the task force would like to offer a careful and judicious review to guide implementation efforts for a standardized and equitable approach to care. The task force understands how high the stakes are for African Americans, recognizes that expeditious recommendations are needed, and that a careful review of the evidence must guide its recommendations. The task force also recognizes that alignment of US clinical laboratories is critical to maintain the success achieved over the past 2 decades in reporting of eGFR, which has improved the quality of care for millions of Americans.

NKF, ASN, and the task force appreciate that issuing recommendations is only the beginning of change. Implementing recommendations of this magnitude will require extensive education and sustained efforts to monitor and assure patient safety and health equity. Assessing the inclusion of race in estimating GFR is part of a larger conversation in addressing racial disparities in kidney health. NKF, ASN, and the task force encourage the community of health care professionals, scientists, medical educators, students, health professionals in training, and patients to join in the larger, comprehensive effort needed to address the entire spectrum of kidney health and to eliminate health disparities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Financial Disclosure:

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Box 1.

Overview of Work Phases and Activities of the NKF-ASN Task Force

Phase 1

- Clarifying the problem and evidence
  - eGFR and measurement
- Race, racism, and genetic ancestry
  - Body composition and populations used in GFR estimation
  - Standardization and guidelines
  - Patients' perspective and shared decision making
- Possible approaches to address race in GFR estimation (Box 3)

Phase 2

- Evaluating the approaches
  - Clinical consequences of different approaches
  - System and societal consequences of different approaches

Phase 3

- Making recommendations
  - Issuance of recommendations
  - Comment on recommendations
  - Implementation

Box 2.

NKF-ASN Task Force Agreed-Upon Statements of Evidence and Value

Equity and Disparities

(1)   Equity[a] in kidney health and kidney health care is a fundamental and important goal. (V)

(2)   Disparities in kidney health and kidney health care should not exist. (V)

(3)   Equity in health care, as defined by the NAM, is care that does not vary in quality on the basis of personal characteristics, such as sex, race/ ethnicity, geographic location, or socioeconomic status.[43] (E)

(4)   A disparity in health care, as defined by NAM, is a difference in care that arises through operation of the health care system; legal or regulatory climate; or discrimination, biases, stereotyping, and uncertainty; but is not due to clinical appropriateness or patient preference.[44] (E)

(5)   A variety of factors influence kidney health across racial and ethnic groups, including delivery of health care, clinical/health policies, environment, genetics, and health behaviors.[45–51] (E) These factors act with a different degree of influence along the life span of individuals and along the continuum from health to kidney disease.[45–49] (E) There are gaps in our understanding of these influences and how to interrupt their effect on creating health disparities.[52] (E) To eliminate disparities, multifaceted initiatives beyond an examination of estimating equations must be developed. (V)

(6)   Differences in health exist across racial and ethnic groups in the United States, and not all of these differences are accounted for by socioeconomic status, geographic regions (including urban versus rural setting), insurance, lifestyle, and clinical factors.[53] (E) Disparities in health care exist across racial and ethnic groups and geographic regions (including urban versus rural setting) in the United States, even after accounting for insurance status, income, age, and disease severity.[44,54] (E)

(7)   Disparities across racial and ethnic groups in the United States exist in kidney disease. These disparities exist with regard to kidney disease risk factors, comorbidities, and progression to kidney failure.[2,5,55] (E) Disparities across racial and ethnic groups in the United States exist in kidney disease care, including diabetes and BP control, nephrology referral, dialysis modality, and transplantation, and with regard to both living and deceased kidney donation.[56–58] (E) Disparities across racial and ethnic groups in the United States in health care exist for diagnostics and therapeutics that rely on GFR assessment (eg, radiocontrast administration; metformin, anticoagulant, and chemotherapeutic use).[59–62] (E)

(8)   Racial and ethnic diversity in participants in health and health care research is an important component of equity for studies and their data to be useful and generalizable to decisions in routine clinical practice.[17,63,64] (E) Research studies should focus on a diversity of racial and ethnic groups to allow for greater generalizability. (V)

Race and Racism

(9)   Race is defined as a construct of human variability based on perceived differences in biology, physical appearance, and behavior.[65] (E) Race and ethnicity are social and not biological constructs.[17,66,67] (E)

(10)   Racism is defined as an organized system, rooted in an ideology of inferiority that categorizes, ranks, and differentially allocates societal resources to human population groups.[68] (E) Racism can be internalized, personal, or institutional.[40] (E) As such, racism can be a part of the environment/ behavior, delivery of health care, and clinical/health policy factors, respectively.[69] (E) Racism can impede prevention and clinical care along the continuum from healthy kidneys, to kidney disease, to treatment.[39,70] (E) Implicit bias has also been shown to negatively affect patient outcomes, particularly among African American patients in the United States.[71] (E) Approaches proven to minimize implicit bias in health care delivery should be used. (V) The effects of racism can be long lasting and this effect may even be carried forward over generations.[72–74] (E)

(11)   Although race and genetic ancestry are related, race captures factors beyond genetic ancestry. The relation between race, ancestry, and observed biology is poorly understood.[17] (E) Research is ongoing to elucidate the relation between genetic ancestry and race.[17] (E)

(12)   According to 2019 US Census population estimates, the self-identified racial and ethnic composition of individuals was 76.3% White, 13.4% African Americans, 5.9% Asian, 1.3% American Indian/Native American and Alaskan Native, 0.2% Native Hawaiian and Other Pacific Islander, with approximately 18.5% Hispanic/Latinx ethnicity.[75] (E) Approximately 2.9% of US individuals self-identified as being of mixed racial background.[75] (E) The complexity of changing racial and ethnic makeup makes the use of race in the practice of medicine challenging and potentially problematic. (V)

GFR Measurement, Estimation, and Equation Performance

(13)   Creatinine and cystatin C are the most commonly used and studied filtration markers for use in estimating GFR.[13] (E) Creatinine is used more commonly, is more widely available, and has a longer history of study than cystatin C.[8,10,76] (E) The determinants of serum concentrations of creatinine are not completely understood, and those of cystatin C are even less well understood.[77] (E) Assays for cystatin C have greater analytical variation than do assays for creatinine.[78] (E)

(14)   Over 250 million serum creatinine measurements are performed each year in the United States. The measurement cost for serum creatinine is currently low relative to serum cystatin C (Medicare reimbursement rates in 2020, \$5.12 and \$18.52, respectively).[79] (E) With more widespread adoption and use of cystatin C, costs could decrease. (V)

(15)   Multiple studies among the US population, including national health statistics studies across age groups, show African American men and African American women have higher serum creatinine concentrations than their White counterparts. Not all factors that might affect serum creatinine concentrations were accounted for in these studies.[7,80] (E) Studies have also shown African Americans have higher serum creatinine concentrations than White individuals at the same measured GFR in the United States.[81] (E) The reasons for these differences are not understood.[81] (E)

(16)   Studies have shown the proportion of African ancestry is related to the level of creatinine in US adults.[82,83] (E) Studies have not examined the relation of genetic ancestry to measured GFR. (E) These studies are desired. (V)

(17)   All estimates of GFR are subject to bias, imprecision, and inaccuracy.[8,10,76,84] (E) Equations should not differentially induce bias and inaccuracy by age, sex, or race; ie, they should not have disproportionate bias, imprecision, or inaccuracy for a particular group according to age, sex, or race. (V)

(18)   Clinical algorithms to assess eGFR with additional predictors are a better indicator of GFR than serum creatinine concentration alone.[13] (E)

(19)   Individual studies of adults with measured GFR and $eGFR_{cr}$ or $eGFR_{cys}$ have been limited in the diversity of participants with regard to age, sex, race, ethnicity, geography, socioeconomic status, comorbidity, and other risk factors for kidney disease. These individual studies have also been limited in diversity of participants with regard to absence, severity, and etiology of kidney disease.[8,10,76,81] (E) Individual studies of adults are also limited in measurements of body composition and chronic or acute illness.[8,12,76] (E) Future studies should seek more diversity in participants with regard to many patient characteristics (age; sex; race; ethnicity; geography; socioeconomic status; comorbidity; risk factors for kidney disease; absence, severity, and etiology of kidney disease; diet; and body composition). (V)

(20)   Estimating equations that were not developed in diverse populations (including race and ethnicity) leads to questions as to how applicable they are to populations not included in the developmental phase without further validation. (V)

(21)   To estimate GFR, it is useful to pool data on participants from individual studies (ie, meta-analysis) to obtain a more comprehensive and diverse sample of people (age; sex; race; ethnicity; geography; socioeconomic status; comorbidity; risk factors for kidney disease; absence, severity, and etiology of kidney disease; and body composition) for whom eGFR can be applied in clinical practice. (V)

(22)   To approximate measured GFR with greater accuracy and to minimize bias in all groups, creatinine-based estimating equations (MDRD and CKD-EPI $eGFR_{cr}$ or $eGFR_{cr-cys}$) have included a coefficient for age, sex, and race; whereas cystatin C–based equations (CKD-EPI) have included coefficients for age and sex alone.[12] (E)

(23)   Data in adult ambulatory outpatients show that the most validated equations (CKD-EPI; $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr-cys}$) perform with different degrees of bias and accuracy.[12] (E) With regard to accuracy, CKD-EPI 2012 $eGFR_{cr-cys}$ has the highest available accuracy (P_{30} at 91.5%), with similar accuracy for CKD-EPI 2009 $eGFR_{cr}$ (at 87.2%) and CKD-EPI 2012 $eGFR_{cys}$ (at 86.9%).[12] (E) Precision (interquartile range) is best for $eGFR_{cr-cys}$ (13.4) and less for $eGFR_{cr}$ (15.4) and $eGFR_{cys}$ (16.4), all in mL/min/1.73 m^2.[12] (E) Bias (measured minus estimated GFR) is similar among equations: $eGFR_{cr-cys}$ (3.9), GFR_{cr} (3.7), and $eGFR_{cys}$ (3.4), all in mL/min/1.73 m^2.[12] (E) Bias and inaccuracy of estimated GFR equations are greater at higher measured GFR.[12] (E) There is no differential accuracy, precision, or bias in equations between Black and non-Black individuals using these equations.[12] (E)

(24)   Inclusion of height and total body weight did not improve performance of eGFR estimation in adults.[11,85] (E) Validated equations for use in children include height, serum creatinine, cystatin C, and SUN, but do not include race.[86] (E) Although methods for measuring body composition have been useful in research settings, no single method has been widely standardized and adapted for routine clinical use for adults in the United States or evaluated for use with eGFR equations. (V)

Laboratory Standardization

(25)   Standardization of measurement and reporting of GFR in the United States is important. (V)

(26)   Standardization can be achieved through issuance and adherence to clinical practice guidelines.[87] (E)

(27)   Reference materials, methods, and accounting for interfering substances are important in achieving assay equivalence.[1,88,89] (E) Results for analytes used to estimate GFR should be standardized. (V)

(28)   Implementation efforts to achieve standardization, and adoption and adherence to practice guidelines, are important for uniform practices. (V)

(29)   Clinical laboratories and the manufacturers of laboratory equipment and supplies must be engaged to achieve standardization. (V)

Patients' Perspective

(30)   Patients prefer to have shared decision making with their physician, rather than the patient or the physician being the sole decision maker.[90] (E) Given the diversity of the patient populations within and across health care settings, patient education on the clinical implications of eGFR should include a discussion on how the equation was derived, its limitations, and how it applies to them. (V)

The task force actively participated in constructing the statements of evidence (E) and value (V), the statements then underwent scrutiny and revision by all of the members of the task force. The task force went through a series of iterations regarding content, language, and perspective.

Abbreviations: BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; $eGFR_{cr}$, estimated GFR from creatinine; eGFRcr-cys, estimated GFR from creatinine and cystatin C; $eGFR_{cys}$, estimated GFR from cystatin C; MDRD, Modification of Diet in Renal Disease (Study); NAM, National Academy of Medicine; P_{30}, accuracy measured as the percentage of estimates within 30% of measured GFR; SUN, serum urea nitrogen.

[a] See Item S2 for terms and definitions.

Box 3.

Inventory of Possible Approaches to Estimating and Reporting GFR for General Use

Creatinine Used as Biomarker	Noncreatinine Biomarker Used
Estimation and reporting with creatinine and race using existing equations	**Estimation with cystatin C, creatinine, and race using existing equations**
(1) eGFR$_{cr}$ (MDRD or CKD-EPI) (age, sex, race) with "Black" estimate reported for self-identified African Americans and "non-Black" estimate reported for persons from other communities[8,10,a]	(13) eGFR$_{cr-cys}$ (CKD-EPI) (age, sex, race) with "Black" estimate reported for self-identified African Americans and "non-Black" estimate reported for persons from other communities[12]
Estimation with creatinine and race using existing equations but reporting without specification of race	**Estimation with cystatin C, creatinine, and race using existing equations but reporting without specification of race**
(2) eGFR$_{cr}$ (CKD-EPI) (age, sex, race) with "Black" estimate reported as "high muscle mass," and "non-Black" estimate reported as "low muscle mass"[a]	(14) eGFRcr-cys (CKD-EPI) (age, sex, race) with "Black" estimate reported as "high muscle mass," and non-Black estimate reported as "low muscle mass"
(3) eGFR$_{cr}$ (CKD-EPI) (age, sex, race) with "Black" estimate reported as "high value," and "White" reported as "low value"[a]	(15) eGFR$_{cr-cys}$ (CKD-EPI) (age, sex, race) with "Black" estimate reported as "high value," and "White" reported as "low value"[a]
(4) eGFR$_{cr}$ (CKD-EPI) (age, sex, race) with the Black coefficient ignored and eGFR value for White/other reported for all	(16) eGFR$_{cr-cys}$ (CKD-EPI) (age, sex, race) with the Black coefficient ignored and eGFR value for White/Other reported for all
(5) eGFR$_{cr}$ (CKD-EPI) (age, sex, race), with the Black coefficient used and eGFR value for African Americans reported for all	(17) eGFR$_{cr-cys}$ (CKD-EPI) (age, sex, race), with the Black coefficient used and eGFR value for African Americans reported for all
(6) Blended eGFR$_{cr}$ (CKD-EPI) (age, sex, race) using a single coefficient weighted for percentage of African Americans in the specific population reported for all	(18) Blended eGFR$_{cr-cys}$ (CKD-EPI) (age, sex, race) using a single coefficient weighted for percentage of African Americans in the specific population reported for all
Estimation with creatinine that do not include race	**Estimation with cystatin C only**
(7) CG estimated creatinine clearance (age, sex, weight)[6,a,b]	(19) eGFR$_{cys}$ (CKD-EPI) (age, sex)[76,a]
(8) eGFR$_{cr}$ (FAS) (age, sex)[91]	(20) eGFR$_{cys}$ (FAS) (age, sex)[92]
(9) eGFR$_{cr}$ (EKFC) (age, sex)[93]	(21) eGFR$_{cys}$ (CAPA) (age)[94]
(10) eGFR (LM) (age, sex)[95]	
Equations to be developed to estimate GFR with creatinine that do not include race	**Equations to be developed to estimate GFR with creatinine and cystatin C that do not include race**
(11) eGFR$_{cr}$ refit without race variable	(22) eGFR$_{cr-cys}$ refit without race variable
(12) eGFR$_{cr}$ refit with height and weight without race variable	
	Estimation with creatinine and cystatin C that does not include race
	(23) eGFR$_{cr-cys}$ (FAS) (age, sex)[92]
	Estimations with new filtration markers in combination with creatinine or cystatin C that do not include race
	(24) eGFR$_{cys-B2M-BTP}$ (age, sex)[96]
	(25) eGFR$_{cr-cys-B2M-BTP}$ (age, sex)[96]

(26) Any of the above either in combination or in sequence with measured GFR using exogenous filtration markers or measured creatinine clearance, to be used generally or by clinical indication (eg, donation, diagnosis, prescription, referral, transplant): Example: One of the above approaches followed by another approach for confirmation.

Parentheses indicate coefficients included in the development of the equation.

Abbreviations: B2M, β_2-microglobulin; BTP, β-trace protein; CAPA, Caucasian and Asian Pediatric and Adult; CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR$_{cr}$, estimated GFR from creatinine; eGFRcr-cys, estimated GFR from creatinine and cystatin C; eGFR$_{cys}$, estimated GFR from cystatin C; EKFC, European Kidney Function Consortium; FAS, full age spectrum; LM, Lund-Malmo; MDRD, Modification of Diet in Renal Disease (Study).

[a]Used or in use in at least one US setting.

[b]CG creatinine clearance is reported in mL/min, eGFR results are standardized (or indexed) to a body surface area of 1.73 m^2 and are reported in mL/min/1.73 m^2.

Box 4.

Sample of Attributes to Be Considered in Making a Recommendation Among Alternative Approaches to Estimation of Kidney Function (Estimated GFR)

• Filtration biomarker availability

• Input variable for computation (race, filtration biomarker, age, sex, body composition measure)

• Representation in development and validation of a diverse population with regard to race, ethnicity, sex, age, body composition, severity and cause of kidney disease, and socioeconomic status

• Bias compared with measured kidney function for different race and ethnic groups

• Accuracy compared with measured kidney function for different race and ethnic groups

• Consequences of equation used for clinical decisions with regard to evaluation and management of patients' kidney function, including health disparities and bias

• Availability of input variables for reporting (race, filtration biomarker, age, sex, body composition measure)

• Feasibility of standardization across the United States

• Patient-centered perspectives on approaches

Table 1.

Topics and Panelists/Discussants During Phase 1

Topic	Moderators and Panelists/Discussants	Location
GFR: history and evolution of kidney function measurement over the past 50 years	**Neil Powe, MD, MPH, MBA; Cynthia Delgado, MD**	
	Andrew S. Levey, MD	Boston, Massachusetts
GFR: measurement, estimation, performance in the United States	**Lesley Inker, MD**	
	Josef Coresh, MD, MPH	Baltimore, Maryland
	Susan L. Furth, MD, PhD	Philadelphia, Pennsylvania
	Andrew S. Levey, MD	Boston, Massachusetts
	Julia B. Lewis, MD	Nashville, Tennessee
	Robert G. Nelson, MD, PhD	Bethesda, Maryland
	Derek K. Ng, PhD	Baltimore, Maryland
	Andrew D. Rule, MD	Rochester, Minnesota
	George Schwartz, MD	Rochester, New York
Race and racism; genetic ancestry and race; creatinine, race and ancestry	**Deidra Crews, MD, ScM**	
	Camara Phyllis Jones, MD, PhD[a]	Atlanta, Georgia
	David R. Williams, PhD[a]	Boston, Massachusetts
	Dorothy E. Roberts, JD[a]	Philadelphia, Pennsylvania
	Nora Franceschini, MD	Chapel Hill, North Carolina
	Alicia R. Martin, PhD	Boston, Massachusetts
	Miriam S. Udler, MD, PhD	Baston, Massachusetts
	Esteban G. Burchard, MD	San Francisco, California
	Jeffery B. Kopp, MD	Bethesda, Maryland
	Opeyemi A. Olabisi, MD, PhD	Durham, North Carolina
Body composition and populations used in eGFR estimation	**Cynthia Delgado, MD**	
	Kamyar Kalantar-Zadeh, MD, PhD	Los Angeles, California
	Andrew D. Rule, MD	Rochester, Minnesota
	Glenn M. Chertow, MD	Palo Alto, California
	Kirsten L. Johansen, MD	Minneapolis, Minnesota

Topic	Moderators and Panelists/Discussants	Location
	Baback Roshanravan, MD	Davis, California
	Flor Alvorado, MD	Baltimore Maryland
	Abinet M. Aklilu, MD	New Haven, Connecticut
Laboratory standardization issues with markers and guidelines	**Greg Miller, PhD; Mukta Baweja, MD**	
	Adeera Levin, MD, FRCPC	Vancouver, British Columbia
	Amy D. Karger, MD, PhD	Minneapolis, Minnesota
	Andrew S. Narva, MD	Washington, DC
	Harvey Kaufman, MD, FCAP, MBA	Short Hills, New Jersey
	Holly J. Kramer, MD, MPH	Maywood, Illinois
	James Fleming, PhD, FACB	Greensboro, North Carolina
	Joseph A. Vassalotti, MD	New York, New York
	Neil Greenberg, PhD, DABCC	Cleveland, Ohio
	Ravi I. Thadhani, MD, MPH	Boston, Massachusetts
	Wolfgang C. Winkelmayer, MD, ScD	Houston, Texas
	W. Greg Miller, PhD	Richmond, Virginia
Patient perspective and participatory decision-making experience and patient-centered considerations	**Glenda Roberts, BSc; Curtis Warfield, MS**	
	Monica Peek, MD, MPH	Chicago, Illinois
	David White	Brooklyn, New York
	Richard Knight	Bowie, Maryland
	Keren Ladin, PhD, MSc	Medford, Massachusetts
	Kevin Fowler, BA	Chicago, Illinois
	Rajnish Mehrotra, MD	Seattle, Washington
	Allison Tong, PhD, MPH[b]	Sydney, Australia
	L. Ebony Boulware, MD	Durham, North Carolina
	H. Gilbert Welch, MD	Boston, Massachusetts
Possible approaches to address race in GFR estimation	**Neil Powe, MD, MPH, MBA; Cynthia Delgado, MD**	
	Task Force Members	

[a] Previously disseminated video talks were reviewed for these individuals due to their availability.

[b] Video talk was reviewed for this individual due to their availability.